CHAPTER 2

Neurobiological and Neurocognitive Alterations in PTSD

A Focus on Norepinephrine, Serotonin, and the Hypothalamic-Pituitary-Adrenal Axis

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Over the past 20 years it has become increasingly clear that dysregulation of multiple neurobiological systems plays an important role in the pathophysiology of posttraumatic stress disorder (PTSD). During situations of threat, parallel activation of numerous brain regions and neurotransmitter systems allows the organism to assess and appropriately respond to situations of potential danger. In the short run, this process serves a protective role and facilitates fleeing from or actively confronting danger. However, for some individuals, long-standing neurobiological responses to fear and stress may prove to be maladaptive and contribute to the development of PTSD (Southwick, Yehuda, & Morgan, 1995).

In this chapter we review data on the relationship between a number of brain regions that are critically involved in the fear response (i.e., prefrontal cortex, amygdala, hippocampus, dorsal raphe nucleus, and locus coeruleus) and three neurotransmitter/neurohormone systems (i.e., noradrenergic system, serotonergic system, and hypothalamic–pituitary–adrenal [HPA] axis) known to be dysregulated in many individuals with PTSD. As such, our review is very limited and does not reflect the enormous complexity of neurobiological responses to danger or neurobiological dysregulations characteristic of PTSD. While this review is based on preclinical and clinical data, much of the discussion on clinical application is speculative in nature.

We begin by briefly reviewing relevant preclinical studies on the relationship between norepinephrine and arousal, sensitization and memory. We then review relevant preclinical studies related to catecholamine regulation of the prefrontal cortex (PFC), locus coeruleus (LC), and amygdala. This is followed by clinical studies on the role of norepinephrine (NE) in combat- and civilian-related PTSD. Next we briefly review preclinical and clinical studies related to the serotonin system and PTSD, with an emphasis on the orbitofrontal cortex. This is followed by a review of the HPA axis as it relates to stress, fear, PTSD, and the PFC and amygdala. Finally, we summarize the data and speculate on possible clinical relevance.

NOREPINEPHRINE

Preclinical Studies

Norepinephrine, Locus Coeruleus, Arousal, and Sensitization

Numerous preclinical studies have shown that central noradrenergic nuclei play an important role in orientation to novel stimuli, alertness, vigilance, selective attention, and cardiovascular responses to life-threatening stimuli (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994). For example, in rats, cats, and monkeys, drowsiness is associated with decreased rate of LC firing while alertness is associated with increased rate of LC firing. Novel sensory stimuli that interrupt ongoing vegetative behaviors (e.g., eating) are particularly likely to provoke rapid activation of the LC. As a result, the organism orients toward the novel stimulus. NE also facilitates selective attention to meaningful stimuli by enhancing excitatory or inhibitory input (signal) relative to basal activity (noise) in the same neuron. At very high rates of LC firing, selective attention is replaced by scanning and vigilance (Aston-Jones et al., 1994).

The LC contains the majority of noradrenergic cell bodies in the brain (Zigmond, Finlay, & Sved, 1995). This large cluster of noradrenergic neurons processes relevant sensory information through its diverse afferent inputs and facilitates anxiety and fear-related skeletomotor, cardiovascular, neuroendocrine, and cognitive responses through its extensive efferent network. Electrical or pharmacological stimulation of the LC elicits fear-related behaviors and increases release of NE in multiple brain regions, such as the amygdala, hippocampus, hypothalamus, and PFC. These brain regions are involved in perceiving, evaluating, remembering, and responding to potentially threatening stimuli. A marked reduction in fear-related behaviors and NE release during threatening situations has been observed secondary to bilateral lesions of the LC (Charney, Deutch, Southwick, & Krystal, 1995; Redmond, 1987).

Catecholaminergic neurons are capable of adjusting level of transmit-

ter synthesis and release depending on current demands and past history (Abercrombie & Zigmond, 1995; Zigmond et al., 1995). For example, dopamine beta-hydroxylase activity, tyrosine hydroxylase, synaptic levels of NE, and LC responsivity to excitatory stimuli all increase when animals are exposed to repeated shock (Irwin, Ahluwalia, & Anisman, 1986; Karmarcy, Delaney, & Dunn, 1984; Melia et al., 1992; Simpson & Weiss, 1994). As a result of these and other adaptations, repeatedly stressed animals may respond to future stressors with exaggerated catecholamine, physiological, and behavioral reactivity (Southwick et al., 1995; Zigmond et al., 1995). This enhanced reactivity, often referred to as stress sensitization, is most likely to follow repeated episodes of uncontrollable, as opposed to controllable, stress. Other neurobiological factors, such as corticotropin-releasing factor (CRF) and neuropeptide Y, have also been implicated in the exaggerated noradrenergic release among animals exposed to chronic uncontrollable stress (Koob, Heinrichs, Menzaghi, Pich, & Britton, 1994; Rasmusson et al., 2000).

Norepinephrine, Amygdala, and Memory

The amygdala is a region of the brain that detects threat and controls defensive responses to these threatening situations. As such, it is involved in both the acquisition and expression of fear (Davis, 1992). The amygdala has strong connections to the hypothalamus and brainstem nuclei that mediate fear responses, including freezing behaviors, alterations in heart rate and blood pressure, sweat gland activity, and release of stress hormones. For example, threat-induced activation of the amygdala stimulates the release of catecholamines and glucocorticoids. Of note, activation of the amygdala by appropriate stimuli can change the neurochemical state of the organism, providing the amygdala with an optimal neurochemical environment for its own function.

In the amygdala, catecholamines also play a central role in the encoding and consolidation of memory for events and stimuli that are arousing, stressful, or fear-provoking. It is well known, for example, that consolidation of recently formed memories can be enhanced by posttraining administration of epinephrine or NE (Gold & Van Buskirk, 1975). These effects are dose and time dependent. The relationship between dose and degree of retention has been described as an inverted "U," where intermediate (but not low or high) doses of epinephrine enhance retention, and the memory-enhancing effects of epinephrine decrease as the time between training and epinephrine administration increases (McGaugh, 2000; Sternberg, Isaacs, Gold, & McGaugh, 1985).

While multiple other stress-induced neuromodulators, such as glucocorticoids, opioid peptides, gamma-aminobutyric acid (GABA), and glucose also affect consolidation of memory for arousing events, they appear

to do so through their influence on activation or inhibition of NE in the amygdala (Introini-Collison, Nagahara, & McGaugh, 1989; McGaugh, 2000). For example, the memory enhancing effects of peripherally administered epinephrine are blocked by posttrial intra-amygdala infusion of propranolol (Liang, Juler, & McGaugh, 1990; Liang, McGaugh, & Yao, 1990), an adrenergic agent that blocks the effects of NE. Epinephrine may also enhance memory consolidation by increasing circulating levels of glucose, which readily crosses the blood–brain barrier (Gold & McCarty, 1995).

Epinephrine and NE additionally have been shown to enhance memory retrieval when administered at the time of memory testing. Stone, Rudd, and Gold (1990) found that epinephrine, amphetamine, and glucose administered 30 minutes prior to retention testing each significantly enhanced memory for a one-trial inhibitory avoidance task, and Sara (1985; Sara & Devauges, 1989) reported that yohimbine and idazoxane, both of which increase central NE, effectively alleviated forgetting. An intact central noradrenergic system appears to be necessary for effective retrieval of emotion-based learning (Sara & Devauges, 1989). It is well known that cues, which are related to the context in which the original learning took place, play an important role in the facilitation of memory retrieval (i.e., state-dependent learning).

Catecholamine Regulation of Amygdala

High levels of catecholamine and cortisol release during stress enhance the functioning of the amygdala, promoting fear conditioning and the consolidation of emotionally relevant memories. For example, fear conditioning is facilitated by dopamine projections to the amygdala (Nader & LeDoux, 1999) involving the D_1 receptor (Greba & Kokkinidis, 2000). Examination of intracellular mechanisms has shown the need for protein synthesis, and the activation of protein kinase A (PKA), protein kinase C (PKC), and mitogen-activated protein kinase (MAPK) signaling pathways (Schafe et al., 2000; Schafe, Nadel, Sullivan, Harris, & LeDoux, 1999; Weeber et al., 2000). In contrast, noradrenergic $alpha_{2A}$ receptor stimulation suppresses fear conditioning and decreases cyclic adenosine monophosphate (cAMP) response element-binding protein (pCREB) expression in the amygdala (Davies et al., 2004).

As noted above, a similar picture has emerged in neurochemical studies of the emotional enhancement of memory consolidation by the basal lateral amygdala. Numerous studies have demonstrated the critical role of NE, with special emphasis on actions at beta-adrenergic receptors (Cahill & McGaugh, 1996). Rodent studies have shown that this beta-adrenergic action is mediated by activation of cAMP/PKA signaling (Roozendaal, Quirarte, & McGaugh, 2002). The beta-adrenergic enhancement of mem-

ory is facilitated by alpha$_1$ adrenoceptor stimulation (Ferry, Roozendaal, & McGaugh, 1999) and by glucocorticoids (Roozendaal et al., 2002). Conversely alpha$_{2A}$ adrenoceptor stimulation reduces the emotional enhancement of contextual memory (Davies et al., 2004).

In summary, the amygdala potentiates the emotional control of behavior. These actions are driven by high levels of catecholamines and glucocorticoid hormones within the amygdala, and reduced by alpha$_{2A}$ adrenoceptor stimulation. The projections of the amygdala to the hypothalamus and catecholamine nuclei likely create a feedforward loop whereby the amygdala can drive its own facilitation during stress exposure. Thus, in general, catecholamines and glucocorticoids enhance amygdala function. Of note, the amygdala can also strongly influence the neurochemical environment in the PFC. Even mild psychological stressors induce high levels of catecholamine release in the PFC, as well as increased circulating corticosterone (Goldstein, Rasmusson, Bunney, & Roth, 1996). These neurochemical responses are abolished by lesions of the amygdala (Goldstein et al., 1996).

Catecholamine Regulation of Prefrontal Cortex

In contrast to their effects in the amygdala, high levels of catecholamines and glucocorticoids greatly *impair* the cognitive functioning of the PFC. The PFC regulates behavior, thought, and affect using representational knowledge (i.e., working memory) (Goldman-Rakic, 1987). The PFC plays an important role in planning, guiding, and organizing behavior. Lesions of the PFC can result in disinhibited behavior, increased motor activity, impaired attention, and diminished ability to inhibit distracting stimuli. Moderate levels of catecholamines are essential to PFC working memory function, but high levels of catecholamines and glucocorticoids impair the working memory functions of the PFC (Arnsten, 2000b). In both rats and monkeys, exposure to mild, uncontrollable stress impairs performance of a working memory task, while having little effect on control tasks with similar motor and motivational demands (Arnsten, 1998b; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996). Dopamine has an important role in this response. For example, stress-induced impairments can be prevented by dopamine D_1 receptor blockade (Arnsten, 1998b; Murphy et al., 1996), and mimicked by infusion of a D_1 agonist into the PFC (Zahrt, Taylor, Mathew, & Arnsten, 1997). Dopamine D_2/D_4 receptors likely contribute as well (Arnsten, 2000a; Druzin, Kurzina, Malinina, & Kozlov, 2000), although this family of receptors has not been studied as thoroughly.

In addition to dopamine, NE plays a critical role in stress-induced PFC dysfunction. Noradrenergic projections from the LC modulate PFC functioning through postsynaptic alpha$_1$ and alpha$_2$ receptors. Preclinical research in rodents and primates suggests that moderate basal release of NE

improves PFC cognitive functioning through preferential binding to postsynaptic alpha$_{2A}$ receptors. Arnsten (Arnsten, 1998a) has proposed that postsynaptic alpha$_{2A}$ receptor stimulation inhibits irrelevant and distracting sensory processing through effects on pyramidal cells that project to sensory association cortices. Inhibition or gating of irrelevant sensory stimuli allows the organism to concentrate on the contents of working memory. However, under stressful conditions (especially uncontrollable stress) when NE release is increased above basal levels in the PFC, postsynaptic alpha$_1$ receptors become activated causing a decline in PFC functioning. It has been proposed that this inhibition of PFC functioning during stressful or dangerous situations has value for survival by allowing the organism to employ rapid habitual subcortical modes of responding (Arnsten, 1998a; Birnbaum, Gobeske, Auerbach, Taylor, & Arnsten, 1999).

Thus, stress-induced PFC dysfunction can be prevented by alpha$_1$ adrenoceptor antagonists such as urapidil and prazosin (Arnsten & Jentsch, 1997; Birnbaum et al., 1999), and mimicked by alpha$_1$ agonist infusion into the PFC in rats (Arnsten, Mathew, Ubriani, Taylor, & Li, 1999) and monkeys (Li, Mao, Wang, & Mei, 1999). More recent research suggests that activation of beta$_1$ adrenoceptors in PFC may also impair working memory (Ramos & Arnsten, unpublished), altbough the mixed beta$_1$/beta$_2$ antagonist, propranolol, has little effect on working memory under nonstress conditions (Arnsten & Goldman-Rakic, 1985; Aston-Jones et al., 1994). The intracellular cascades initiated by high levels of catecholamines in PFC have just begun to be examined. Evidence to date indicates that activation of both cAMP/PKA (Arnsten et al., 1999) and PKC (Birnbaum et al., 2004) intracellular signaling cascades contribute to PFC cognitive impairment during stress.

In contrast to noradrenergic actions at alpha$_1$ and beta$_1$ receptors, stimulation of alpha$_2$ adrenoceptors protects PFC cognitive function during stress. The alpha$_2$ agonist, guanfacine, was more potent than clonidine in protecting against stress-induced PFC dysfunction (Birnbaum, Podell, & Arnsten, 2000). As clonidine is more potent than guanfacine at presynaptic alpha$_2$ receptors, these results suggest that postsynaptic alpha$_2$ receptors play an important protective role. Studies of genetically altered mice have confirmed that working memory enhancement results from actions at alpha$_{2A}$ adrenoceptors (Franowicz et al., 2002), and infusion of the alpha$_{2A}$ agonist, guanfacine, directly into monkey PFC produces a delay-related enhancement of working memory (Li et al., 1999). Alpha$_{2A}$ adrenoceptor stimulation likely strengthens PFC function by reducing cAMP/PKA signaling (Ramos & Arnsten, unpublished).

The strengthening of PFC function by alpha$_{2A}$ receptor stimulation has been observed at the cellular level as well. PFC neurons can fire during the delay interval, representing information in the absence of environmental

stimulation (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster, 1973) and despite the presence of distractors (Miller, Li, & Desimone, 1993). Delay-related firing also contributes to behavioral inhibition such as the ability to suppress a prepotent response (Funahashi, Chafee, & Goldman-Rakic, 1993). Thus, it is of great interest that $alpha_2$ adrenoceptor stimulation increases the delay-related firing of PFC cells (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). Conversely, yohimbine, an $alpha_2$ adrenergic receptor antagonist that increases the release of NE, impairs working memory (Aston-Jones et al., 1994) and reduces delay-related firing (Anderson et al., 1999; Sawaguchi, 1998). In sum, $alpha_{2A}$ adrenoceptor stimulation strengthens PFC function, while $alpha_1$, $beta_1$, and high levels of D_1 receptor stimulation impair PFC function.

In this context, it is important to note that NE has higher affinity for $alpha_{2A}$ receptors (O'Rourke, Blaxall, Iversen, & Bylund, 1994) than for $alpha_1$ receptors (Mohell, Svartengren, & Cannon, 1983) or beta receptors (Pepperl & Regan, 1994). Therefore, conditions of modest NE release (i.e., during alert but nonstressful wakefulness) would predominantly engage $alpha_{2A}$ adrenoceptors, facilitating PFC regulation of behavior, and suppressing the role of the amygdala. In contrast, high levels of NE release during stress would engage $alpha_1$ and beta adrenoceptors, impairing PFC function and promoting amygdala regulation of behavior. In this way NE can act as a chemical switch, determining which brain structures have control over our behavior.

In summary, during uncontrollable stress, the amygdala induces the release of high levels of catecholamines and cortisol, thus optimizing its own neurochemical environment while impairing PFC regulation of behavior, thought, and affect. It is important to note that the PFC has extensive projections to the amygdala (Ghashghaei & Barbas, 2002), and can potently inhibit amygdala function (Quirk, Likhtik, Pelletier, & Pare, 2003). Thus, when the amygdala floods the PFC with catecholamines and takes the PFC "off-line," it also releases PFC inhibition of the amygdala and sensorimotor cortex, diminishing rational influences on behavior and thought.

Clinical Studies

General

A large body of clinical physiological, neuroendocrine, receptor binding, pharmacological challenge, brain imaging, and pharmacological treatment studies have provided compelling evidence for exaggerated noradrenergic activity in traumatized humans with PTSD (Friedman & Southwick, 1995; Southwick et al., 1999a). This exaggerated activity is generally observed in response to a variety of stressors but not under baseline or resting condi-

tions. It has been suggested that altered reactivity of noradrenergic neurons is associated with a variety of hyperarousal and reexperiencing symptoms characteristic of PTSD (Southwick et al., 1999a).

Baseline Norepinephrine

Most studies measuring baseline or resting indices of catecholamine activity have found insignificant differences between subjects with PTSD and control groups. This includes psychophysiology studies, which compare indices of resting heart rate, blood pressure and galvanic skin conductance as well as neuroendocrine studies measuring plasma NE and epinephrine. (Southwick et al., 1999a, 1999b). For example, in a large multicenter psychophysiology study, Keane et al. (1998) reported no differences between baseline heart rate, blood pressure, and galvanic skin response between Vietnam combat veterans with PTSD, Vietnam combat veterans without PTSD, and healthy controls. Similarly, at least three studies of combat veterans with PTSD have reported resting plasma levels of NE that did not differ from levels in healthy controls (reviewed in Southwick, 1999a).

24-Hour Urine Catecholamines and Platelet Adrenergic Receptors

Unlike baseline psychophysiology and neuroendocrine data, studies of 24-hour plasma NE levels, 24-hour urine hormone excretion, and platelet adrenergic receptor number have found significant differences between subjects with PTSD and controls (Southwick et al., 1999a). Under resting or unstimulated conditions, Yehuda et al. (1998) sampled plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) and NE over a period of 24 hours in subjects with PTSD compared to healthy controls and found significantly higher mean NE levels in combat veterans with PTSD compared to combat veterans with PTSD and comorbid depression, patients with MDD alone, and healthy controls. There were no differences in MHPG between groups.

Most studies of combat veterans and civilians (e.g., residents living near the Three Mile Island Nuclear Power Plant accident) (Davidson & Baum, 1996); and of women with histories of child abuse (Limieux & Coe, 1995) have found elevated 24-hour urine excretion of NE in subjects with PTSD compared to controls. It is possible that 24-hour catecholamine levels reflect the summation of both phasic physiological changes in response to meaningful stimuli and tonic resting levels of catecholamines, while single plasma samples reflect only tonic activity (Southwick et al., 1999a, 1999b).

Reduced platelet alpha$_2$-adrenergic receptor number has been reported in combat veterans and traumatized children with PTSD compared to healthy controls (Perry, 1994). It has been hypothesized that down-

regulation of alpha$_2$-adrenergic receptors serves as an adaptive response to chronic elevation of circulating catecholamines. This hypothesis is consistent with the finding that patients with congestive heart failure and hypertension (conditions characterized by chronic elevated levels of plasma catecholamines) also have reduced numbers of platelet alpha$_2$ receptors.

Catecholamine Challenge Paradigms

Studies that challenge catecholamine systems have been designed to evaluate catecholamine activity under controlled conditions where the subject is intentionally exposed to provocative auditory or visual stimuli or exogenously administered biological substances, such as lactate or yohimbine. Challenge paradigms using platelets and lymphocytes have also been used to assess adrenergic receptor reactivity.

A review of the scientific literature suggests that trauma survivors witb PTSD experience greater physiological reactivity (particularly heart rate) in response to trauma-relevant stimuli than do trauma survivors without PTSD and nontraumatized healthy controls. Trauma-relevant stimuli have included sights and sounds of combat as well as scripts of personally experienced traumas. In all published studies approximately two thirds of PTSD subjects have demonstrated exaggerated reactivity to trauma-associated cues. The percentage appears to be even higher in subjects with severe PTSD (Keane et al., 1998; Orr, 1997a; Orr et al., 1997b). On the other hand, most studies have found that subjects with PTSD do not experience exaggerated physiological reactivity in response to generic non-trauma-related stimuli (Orr, 1997a). Of note, a relationship between physiological reactivity to traumatic cues and elevation in endogenous catecholamines has been supported by McFall, Murburg, Ko, and Veith (1990), who found parallel increases in subjective distress, blood pressure, heart rate, and plasma epinephrine among combat veterans with PTSD in response to viewing a combat film. Similar findings have been reported by Blanchard, Kolb, Prins, Gates, and McCoy (1991) with respect to heart rate and plasma NE.

In a study designed to assess dynamic functioning of alpha$_2$ receptors, Perry (1994) incubated intact platelets with high levels of epinephrine and found a greater and more rapid loss in receptor number among subjects with PTSD compared to controls, suggesting that alpha$_2$ adrenergic receptors in subjects with PTSD were particularly sensitive to stimulation by the agonist epinephrine. Challenge studies assessing epinephrine on forskolin-stimulated adenylate cyclase activity and the lymphocyte beta-adrenergic receptor-mediated cyclic adenosine 3'5'-monophosphate system in subjects with PTSD have been mixed (Southwick et al., 1999a).

While a number of pharmacological challenges have been used in the

study of PTSD, investigations employing yohimbine have been most relevant to understanding catecholamine systems. Yohimbine is an alpha$_2$-adrenergic receptor antagonist that increases presynaptic release of NE by blocking the alpha$_2$-adrenergic autoreceptor. When administered to healthy subjects, yohimbine has few effects. However, subjects diagnosed with panic disorder experience marked yohimbine-induced increases in subjective anxiety, heart rate, and biochemical indices of noradrenergic activity. Additionally, approximately 60% experience yohimbine-induced panic attacks. Similarly, in subjects with PTSD, yohimbine causes significant increases in subjective anxiety, heart rate, and plasma MHPG, a metabolite of NE. In one study (Southwick et al., 1993), 70% of combat veterans with PTSD experienced yohimbine-induced panic attacks. However, unlike panic disorder patients, subjects with PTSD also experienced marked increases in yohimbine-induced PTSD symptoms such as hypervigilance and intrusive memories. In fact, nearly 80% of combat veterans with PTSD, when administered yohimbine, experience vivid intrusive memories of combat traumas and 40% experienced yohimbine-induced flashbacks.

In the above cited study, it is possible that yohimbine-induced increases in NE impaired PFC functioning, which contributed to intrusive memories among individuals with PTSD. These intrusive memories and flashbacks were accompanied by increased heart rate and catecholamine activity (i.e., increased plasma MHPG). The retrieval of traumatic memories secondary to yohimbine infusion is consistent with animal studies demonstrating enhanced retrieval of aversive memories through adrenergic and noradrenergic stimulation (Conway, Anderson, & Larsen, 1994). Creating a biological context (yohimbine-induced increase in catecholamine activity) that resembles the biological state at the time of encoding (fear-enhanced increase in catecholamine activity) may have served to facilitate the retrieval of frightening memories (state-dependent recall).

Forty percent of PTSD subjects who received IV yohimbine also experienced full-blown flashbacks. It is possible that impaired PFC functioning (secondary to exaggerated release of NE and engagement of postsynaptic alpha$_1$ receptors) may have compromised a number of executive functions, such as simulation and reality testing, that are needed to differentiate past experiences from experiences occurring in the present. Simulation involves the generation of internal models of reality while reality testing includes the monitoring of information sources. Thus, elevated NE in the amygdala and hippocampus may have facilitated retrieval of past memories but deficits in simulation and reality testing may have made it difficult to discriminate between the current external world and the internally generated memory of the past. The result may have been a flashback where the past memory was experienced as if it were occurring in the present.

This model is consistent with results from a recent positron emission

tomography (PET) study where healthy controls had increased yohimbine-induced metabolism and PTSD subjects decreased yohimbine-induced metabolism in neocortical brain regions (orbitofrontal cortex, temporal cortex, PFC, parietal cortex). It is possible that yohimbine-induced release of NE (which was greater in PTSD subjects compared to controls) in the PFC resulted in exaggerated alpha$_1$ adrenergic receptor occupancy with a subsequent decrease in regional metabolism.

Of course, genetic factors clearly play a role in sympathetic nervous system (SNS) reactivity to stress. Recent evidence suggests that alpha$_2$ adrenoreceptor gene polymorphisms may play a role in baseline catecholamine levels, intensity of stress-induced SNS activation, and rate of catecholamine return to baseline after stress. In a study of healthy subjects, homozygous carriers for the alpha$_2$cDel322-325-AR polymorphism had exaggerated total body noradrenergic spillover at baseline, exaggerated yohimbine-induced increases in anxiety and total body noradrenergic spillover, and a slower than normal return of total body noradrenergic spillover to baseline after yohimbine infusion (Neumeister et al., in press). Such individuals may be more vulnerable to stress-related psychiatric disorders such as PTSD and depression.

SEROTONIN

General Characteristics and Relevant Brain Regions

Serotonin is a monoamine that is synthesized from tryptophan in serotonergic neurons within the brain and gastrointestinal tract. Neurons that synthesize and release serotonin are found almost exclusively in the raphe nuclei of the brainstem (Nestler, Hyman, & Malenka, 2001). Serotonergic neurons project to many brain regions including limbic structures and all areas of the cerebral cortex (Nestler et al., 2001). Serotonin receptors (14 receptor subtypes) can be found in multiple brain regions including the PFC, amygdala, LC, hippocampus, dorsal raphe nucleus, nucleus accumbens, and hypothalamus. The serotonergic system is a complex system that has both inhibitory and excitatory actions.

Serotonin is specifically known to play an important role in regulation of the PFC, the amygdala, and the hippocampus, each of which has been implicated in the pathophysiology of PTSD. These three brain regions have intricate neuroanatomical connections with one another and with other structures, such as the LC, which appear to be involved in the pathophysiology of PTSD. The hippocampus receives projections from brainstem regions (LC, raphe nucleus, ventral tegmental area), the amygdala, and the cortex. Major hippocampal efferents project to the amygdala, hypothalamus, and septum (Clark & Boutros, 1999). The amygdala is divided into

three nuclei, and receives inputs from various areas including the PFC, cingulate gyrus, and ventral striatum. All three nuclei have connections with the hypothalamus for expression of emotion by way of the autonomic and endocrine systems (Clark & Boutros, 1999).

Relationship to Orbitofrontal Cortex

The effects of serotonin on prefrontal cortical function are still under investigation, and likely very complex given the large number of serotonin receptors. Mounting evidence suggests that serotonin may play an important role in orbitofrontal cortical functioning. The orbitofrontal cortex is known for its role in filtering, processing, and evaluating social and emotional information. It assists in evaluating cues within a social context and in interpreting the emotional properties of stimuli. It also plays a role in the emotional processing of affective memories. These functions are believed to be important for social and emotional decision making. Patients with damage to the orbitofrontal cortex tend to have deficits in social decision making and difficulty inhibiting inappropriate social responses, including aggressive impulses. They often demonstrate behaviors marked by impulsivity and aggression (Blair, Morris, Frith, Perrett, & Dolan, 1999). In addition, orbitofrontal damage can result in impaired recognition of emotions in others. Accurate recognition of emotional stimuli and drawing on emotional memory is important for the appropriate modulation of behavioral responses to a host of everyday situations.

The effects of serotonin on orbitofrontal function have been examined in a series of tryptophan-depletion studies. Tryptophan depletion involves the oral administration of a drink mixture of 15 large neutral amino acids without tryptophan. Ingestion of a tryptophan depleting drink mixture, followed by a low-tryptophan diet, has been shown to reduce plasma tryptophan in humans by over 80%, which subsequently causes a transient depletion of 5-HT stores by approximately 50% (Young, Smith, Phil, & Ervin, 1985). Tryptophan-depletion studies have demonstrated that low serotonin levels are associated with impairment in a number of psychological tasks, including reversal learning (Park et al., 1994; Young et al., 1985). Reversal tasks measure an individual's ability to evaluate, integrate, and act on environmental cues. More specifically, reversal tasks require an individual to stop responding to a stimulus that previously has been reinforced and begin responding to a previously non-reinforced stimulus in order to receive a reward (Robbins & Everitt, 1995).

Optimal performance on reversal-learning tasks requires intact serotonergic innervation of an intact orbitofrontal cortex. Performance on these tasks is impaired in animals with lesions of the orbitofrontal cortex (Dias, Roberts, & Robbins, 1996a), in humans with damage to the

orbitofrontal cortex, and in humans whose serotonin has been depleted (Rolls, Hornak, Wade, & McGrath, 1994). While the effects of serotonin are probably not specific to the orbitofrontal cortex, the orbitofrontal cortex (compared to the dorsolateral cortex) may be especially sensitive to the effects of serotonin (Park et al., 1994).

Studies in individuals with PTSD have demonstrated alterations in both serotonergic function and in orbitofrontal cortex-mediated tasks, as reflected by impaired ability to perform object-alteration and reversal tests. Regarding the orbitofrontal cortex, Koenen et al. (2001) reported impaired performance on object alteration and reversal learning in combat veterans with PTSD. Among women with PTSD, Bremner et al. (2003) found decreased regional cerebral blood flow (rCBF) in areas of the PFC (including the orbitofrontal cortex) during retrieval of emotionally balanced word pairs. Additionally, a number of symptoms that are commonly observed in patients with PTSD, including misinterpretation of emotionally laden cues, impulsivity, aggression, and enhanced emotional memory have been described in patients with orbitofrontal cortex lesions. Receptor, challenge, and pharmacological treatment studies have all implicated altered serotonin function in the pathophysiology of PTSD. The above findings suggest that deficits in object alteration and reversal learning among individuals with PTSD might, in part, reflect altered serotonin modulation of the orbitofrontal cortex.

Relationship to the Amygdala and Locus Coeruleus

Serotonin also affects the amygdala. Reduced levels of serotonin in the amygdala have been associated with a decrease in threshold of amygdala firing (i.e., increased activation of the amygdala) through effects on GABAergic interneurons, which modulate glutamatergic input (Morgan, Krystal, & Southwick, 2003). Furthermore, the ability of 5-HT to modulate glutamatergic activity is dependent on the presence of corticosterone (Stutzmann & LeDoux, 1999; Stutzmann, McEwen, & LeDoux, 1998). On the other hand, increased 5-HT has been found to increase the threshold of amygdala firing with a resultant decrease in vigilance and fear-related behaviors. Efficacy of selective serotonin reuptake inhibitors (SSRIs) in patients with PTSD may be related, in part, to an increased threshold of amygdala firing.

Serotonin also has important effects on the LC. An inhibitory role of 5-HT on LC and NE neurons has been demonstrated in lesion, electrophysiological, and biochemical studies (Aston-Jones et al., 1991; Bobker & Williams, 1989). For example, lesions of the raphe nuclei as well as pretreatment with 5-HT synthesis inhibitors (which effectively release inhibitory control of the LC by 5-HT) have been shown to increase tyrosine hy-

droxylase activity and firing rate of LC/NE neurons in the LC. More specifically, in rats with lesions of 5-HT neurons, firing activity of NE neurons is approximately 50% greater than that recorded in intact animals (Blier, 2001). In a related study, prolonged administration of the SSRI citalopram (14 and 21 days) led to a progressive decrease in the firing activity of NE neurons (Blier, 2001).

The interaction between serotonin and NE has also been studied in healthy humans. In order to assess the modulating effects of 5-HT on NE, 11 healthy human subjects were depleted of tryptophan and then administered yohimbine, an alpha$_2$-adrenergic antagonist (Goddard et al., 1995). In separate studies, tryptophan depletion has been shown to cause mild decreases in mood and concentration among healthy subjects while a clinically significant worsening of depressive symptoms has been observed in remitted patients on antidepressants (Delgado et al., 1990; Young et al., 1985). Yohimbine administration has produced modest or no increase in subjective nervousness among healthy subjects, but in patients with panic disorder, yohimbine has caused marked increases in symptoms consistent with anxiety and panic as well as elevations on physiological and neuroendocrine measures associated with heightened arousal and anxiety (Charney, Woods, Krystal, Nagy, & Heninger, 1992). In Goddard's tryptophan–yohimbine study, healthy subjects who underwent tryptophan depletion and then received yohimbine experienced a synergistic increase in subjective nervousness compared to administration of either yohimbine alone or a placebo (Goddard et al., 1995). Tryptophan depletion caused a marked reduction in 5-HT, which in turn left the noradrenergic response to yohimbine partially unchecked.

Relationship to Clinical Symptoms

Alterations in serotonin have been implicated in PTSD as well as in disorders of mood, impulsivity, and aggression. It is likely that the effects of altered serotonergic function among subjects with PTSD are mediated by multiple brain regions known to be involved in central fear circuitry. Preclinical and clinical data have shown that alterations in serotonin affect orbitofrontal cortex functioning, orbitofrontal cortex inhibition of the amygdala, threshold of amygdala firing, and the firing rate of the LC. It is possible that these alterations contribute to a number of symptoms commonly described in PTSD. For example, serotonin's effect on orbitofrontal cortex might contribute to misinterpretation of emotion-laden stimuli including accurate recognition of emotions in others, impulsivity and aggression, and socially inappropriate decision making. Alterations in serotonin also contribute to exaggerated alerting and fear-related behaviors through release of orbitofrontal cortex inhibitory control of the amygdala, effects

on GABAergic interneurons within the amygdala, and diminished tonic inhibition of LC/NE firing.

Despite the above evidence, which implicates serotonin in the pathophysiology of multiple symptoms commonly seen in trauma victims with PTSD (i.e., aggression, impulsivity, depression), relatively little research to date has actually investigated serotonergic function in subjects with PTSD per se. Several reports of baseline serotonergic function in PTSD have reported decreased platelet uptake in subjects with PTSD (Arora, Fichtner, O'Connor, & Crayton, 1993; Bremner, Southwick, & Charney, 1999). A number of studies have also used challenge paradigms to assess serotonergic activity in trauma victims with PTSD. Davis, Clark, Kramer, Moeller, and Petty (1999) in a study of combat veterans with PTSD, reported a blunted prolactin response to the serotonin-releasing and uptake inhibitor D-fenfluramine. In a study comparing the effects of the noradrenergic probe yohimbine to the serotonergic probe MCPP, 40% of combat veterans with PTSD experienced a panic attack in response to yohimbine and 30% in response to MCPP (Southwick, Bremner, Rasmusson, Morgan, Arnsten, & Charney, 1999a). This study provided preliminary evidence for possible neurobiological subgroups of patients with PTSD, one showing increased reactivity of the noradrenergic system and the other increased reactivity of the serotonergic system.

Further evidence that indirectly supports a role for serotonin in the pathophysiology of PTSD comes from studies in subjects with aggression, impulsivity, and depression. These include reduced cerebrospinal fluid (CSF) 5-HIAA in aggressive psychiatric patients, impulsive violent men, and suicide victims who have killed themselves through violent means (Davidson, Putnam, & Larson, 2000). Genetic evidence includes the relationship between a polymorphism in the gene that codes for tryptophan hydroxylase and individual differences in aggressive behavior (Manuck et al., 1999; Nielsen et al., 1994). The link between genetic predisposition for altered serotonergic function and life traumas has been further demonstrated in a recent study by Caspi et al. (2003) who found that one or two copies of the short allele of the 5-HT transporter promoter polymorphism, in association with a life stress, significantly increased the risk for developing depression, a disorder that frequently accompanies PTSD.

Perhaps the strongest clinical evidence speaking to serotonin's role in PTSD comes from pharmacological treatment studies. Currently only two medications have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of PTSD. Both agents, sertraline and paroxetine, are SSRIs. In large multicenter treatment trials, these agents have been shown to significantly improve all three PTSD symptom clusters (re-experiencing, avoidance, arousal), when compared to placebo. Additionally monoamine oxidase inhibitors, which increase serotonin by inhibiting its

degradation, have shown promise in treating trauma victims with PTSD (Foa, Keane, & Friedman, 2000).

THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

General Characteristics

Alterations in HPA-axis functioning have been reported in patients diagnosed with PTSD. In response to acute and chronic stress, the paraventricular nucleus of the hypothalamus secretes corticotropin-releasing factor (CRF), which, in turn, stimulates the anterior pituitary gland to synthesize and release adrenocorticotropin (ACTH). ACTH then stimulates the synthesis and release of adrenal cortical glucocorticoids. Cortisol mobilizes and replenishes energy stores, inhibits growth and reproductive systems, contains the immune response, and affects behavior through actions on multiple neurotransmitter systems and brain regions.

Relationship to Amygdala and Prefrontal Cortex

As previously noted, threat activates the amygdala. The amygdala, in turn, projects to the hypothalamus, which activates the pituitary and adrenal glands. Glucocorticoids (cortisol in humans and corticosterone in many animals) that are released by the adrenal gland then cross the blood–brain harrier and exert effects on the amygdala and PFC. While high levels of glucocorticoids facilitate functioning of the amygdala, they impair functioning of the PFC. For example, systematic administration of glucocorticoids or local glucocorticoid infusion into the PFC has been shown to impair working memory (Roozendaal, McReynolds, & McGaugh, 2004). Further, high levels of glucocorticoids in the PFC are known to augment synaptic catecholamine levels via blockade of catecholamine reuptake (Grundemann, Schechinger, Rappold, & Schomig, 1998). The result is impaired working memory and decreased cortical inhibition of limbic activity. The combination of glucocorticoid-mediated enhancement of amygdala functioning (e.g., fear conditioning and consolidation of emotional memory) and glucocorticoid-mediated impairment in PFC functioning can leave the organism in a physiological state dominated by poorly inhibited limbic reactivity.

Cortisol and PTSD

The above preclinical findings suggest that abnormal CNS cortisol levels among individuals with PTSD may contribute to some of the deficits in cognitive functioning that have been observed in this patient population.

However, the HPA axis is complex and findings to date in subjects with PTSD have been both inconsistent and, at times, difficult to interpret. Thus, a clear association between abnormalities in the HPA axis and cognitive dysfunction in PTSD has not yet been clearly established.

Although a number of studies have found decreased 24-hour urine cortisol levels, others have reported elevated levels. For example, studies of HPA-axis function in male veterans have produced mixed findings with some showing low, some similar, and some high 24-hour urine cortisol levels in veterans with PTSD compared to combat veterans and healthy controls without PTSD (reviewed in Rasmusson et al., 2003). Similarly, studies of premenopausal women and children with PTSD have reported increased 24-hour urinary cortisol output, apparently related to increased pituitary adrenocorticotropic hormone and adrenal cortisol reactivity. In contrast, a study performed in postmenopausal female survivors of the Holocaust showed decreased 24-hour urinary cortisol output, as did a study in male Holocaust survivors. Insufficient control for nicotine, psychotropics, and alcohol use by PTSD subjects may have contributed to inconsistent findings across studies (reviewed in Rasmusson et al., 2003). In addition, it is possible that genetic factors may have contributed to variable findings. For instance, functional mutations in the 21-hydroxylase gene, frequently present in some ethnic groups, are associated with diminished cortisol synthesis (Witchel, Lee, Suda-Hartman, Trucco, & Hoffman, 1997).

Of note, however, Baker and colleagues (1999) found that CSF cortisol levels in male veterans with chronic PTSD were high even when their urinary cortisol levels were not different from healthy controls. These data suggest that urinary cortisol levels may not always adequately reflect the level of glucocorticoid exposure experienced in the central nervous system. Other evidence of hyperactive or sensitized HPA activity in individuals with PTSD is reviewed by Yehuda (2002).

Dehydroepiandrosterone and Frontal Cortex

Cortisol is not the only adrenal neuroactive steroid of potential relevance to functioning of the frontal cortex. Dehydroepiandrosterone (DHEA) is another steroid that is secreted from the adrenal gland episodically and synchronously with cortisol in response to fluctuating ACTH levels (Rosenfeld et al., 1971). Indeed, DHEA derived from the periphery is thought to be the primary source of DHEA in the brain (Compagnone & Mellon, 2000). DHEA and its sulfated metabolite, DHEAS, have antiglucocorticoid effects and positively modulate *N*-methyl-*D*-aspartate (NMDA) receptor function and antagonize $GABAA_A$ receptor-mediated chloride ion flux (Baulieu & Robel, 1998). As a result, DHEA would be expected to enhance monoaminergic responses during initial traumatic stress exposure

or during reexposure to cues previously associated with traumatic experiences.

It is of interest that higher DHEA and/or DHEAS levels have been observed in Israeli combat veterans with PTSD compared to Israeli veterans without PTSD (Spivak et al., 2000) while DHEAS levels have been found to rise over several months in association with the development of PTSD among Kosovo refugees (Sondergaard, Hansson, & Theorell, 2002). In addition, Rasmusson and colleagues (2004) found that DHEA responses to maximum stimulation of the adrenal gland during an ACTH stimulation test were significantly increased in premenopausal women with PTSD. Interestingly, the magnitude of the DHEA response to ACTH was inversely related to PTSD symptoms as measured by the Clinician Administered PTSD Scale (CAPS). This relationship was explained primarily by a negative relationship between DHEA reactivity and avoidance or hyperarousal symptoms of PTSD.

The study by Rasmusson et al. (2004) showing a negative relationship between the adrenal capacity for DHEA release and PTSD symptoms suggested that DHEA may confer resistance to some of the disabling effects of traumatic stress exposure, perhaps in part by enhancing frontal lobe functioning. This possibility is supported by the work of Morgan et al. (2004) showing a negative relationship between the ratio of plasma DHEAS/cortisol levels and dissociation as well as a positive relationship between the DHEAS/cortisol ratio and behavioral performance during severe acute stress in apparently healthy military personnel undergoing survival training. In contrast, low levels of DHEA(S) alone or in relation to cortisol have been repeatedly associated with depressed mood and reduced feelings of vigor and well-being, while DHEA itself has been found to effectively treat at least a subpopulation of patients with refractory major depression, a condition known to be associated with deficiencies in frontal lobe processing. And finally, a recent study by Strous et al. (2003) found that DHEA reduced negative symptoms of schizophrenia without worsening positive symptoms when administered in addition to the subjects' usual medication regimens.

DHEA(S) may directly affect frontal lobe function through modulation of GABAergic and NMDA receptor function as well as indirectly through secondary effects on monoamine release. In addition, DHEA may indirectly promote optimum frontal lobe function through effects in the amygdala. Activation of NMDA receptors in the amygdala has been found to facilitate extinction as well as formation of conditioned fear-based memories (Walker & Davis, 2002). Thus, heightened DHEA release in the period following trauma exposure when natural extinction occurs in some individuals or during exposure-based therapy may promote extinction and prevent future disruption of frontal lobe function by catecholamine fluxes induced by

trauma-related cue exposure. It is also possible that "antiglucocorticoid" effects exerted by DHEA in many tissues including brain may be found to pertain specifically to the frontal cortex. Thus far, however, research has focused on the hippocampus where hydroxylated metabolites of DHEA have been shown to interfere with the nuclear uptake of activated glucocorticoid receptors (Morfin & Starka, 2001).

Neuroactive Steroids and Activation of the Hypothalamic-Pituitary-Adrenal Axis

Adrenally derived neuroactive steroids that positively modulate $GABA_A$ receptors and enhance chloride flux into neurons also deserve mention, with allotetrahydro-deoxycorticosterone and allopregnanolone being the most potent of these (Compagnone & Mellon, 2000). Recent data show allopregnanolone levels in the CSF of premenopausal women in the follicular phase of the menstrual cycle to be about 50% lower than in healthy nontraumatized women (Rasmusson, Pinna, Weisman, Gottschalk, Charney, Krystal, et al., 2005). Allopregnanolone is released by the adrenal gland in response to stress and is thought to provide delayed negative feedback inhibition of the HPA axis as well as exert anxiolytic and anesthetic effects. Thus, reductions in this neuroactive steroid may prolong activation of the HPA axis and promote the enhancement of monoamine effects in the frontal lobe and amygdala by DHEA and cortisol. As noted above, under such conditions, amygdala-mediated defense responses and sensory processing would be expected to hold sway over cognitive and behavioral functions subserved by frontal-lobe-mediated working memory.

Gene Polymorphisms and Responses to Trauma

There are many points at which variations in genetic endowment or stress-induced alterations in gene regulation could affect biosynthesis or degradation of adrenally derived neuroactive steroids. Indeed, there are more than 65 different functional mutations of the 21-hydroxylase gene already known to affect cortisol production. Other HPA-axis-related genes with polymorphisms known to enhance either ACTH or cortisol responses to stress include the catechol-O-methyltransferase (COMT) gene (Hernandez-Avila, Wand, Luo, Gelernter, & Kranzler, 2003; Oswald, McCaul, Choi, Yang, & Wand, 2004), angiotensin I-converting enzyme (ACE-I) gene (Baghai et al., 2002), the glucocorticoid receptor gene (Wust et al., 2004), the ACTH gene (Slawik et al., 2004) and the CRF or CRF receptor gene (Challis et al., 2004; Gonzalez-Gay et al., 2003; Kyllo et al., 1996; Smoller et al., 2003). No doubt others will be identified in the near future. Assessment of the effects of functional mutations of such genes on other

neuroactive steroids including DHEA, allopregnanolone, and allotetrahydrocorticosterone in addition to ACTH and cortisol will likely be important in understanding individual variability in acute cognitive reactions to traumatic stress and cognitive dysfunction subsequent to trauma. In addition, it will be important to understand epigenetic factors that regulate the function of such genes. Hopefully, this line of research will promote our understanding of HPA-axis-related risk factors that predispose to stress-induced dysregulation of frontal lobe function and also lead to the development of novel strategies for the prevention or treatment of PTSD and PTSD-related disabilities.

CONCLUSIONS AND IMPLICATIONS

In summary, we have briefly reviewed preclinical and clinical data related to three neurotransmitter/neuroendocrine systems that are known to be involved in the pathophysiology of PTSD and that may contribute to some of the symptoms and neurocognitive deficits that have been reported in this patient population. These neurotransmitters appear to exert their stress-related effects through actions in multiple brain regions including the PFC, amygdala, hippocampus, dorsal raphe nucleus, and the LC.

As noted earlier, stress sensitization of noradrenergic systems results in increased synthesis and release of NE. When stress-sensitized organisms are subsequently stressed, the amygdala and the PFC become flooded with NE. In the PFC, high levels of NE preferentially engage postsynaptic alpha$_1$ receptors, which in essence take the PFC "off-line." In humans with PTSD, impairment in PFC functioning would likely compromise executive functioning and decrease inhibitory control of the amygdala with a resultant increase in fear-related behavior (Davis, 1999).

It is possible that PFC functioning might also be affected by alterations in serotonin, cortisol, and DHEA among subjects with PTSD. For example, decreased serotonergic stimulation of the orbitofrontal cortex would be expected to impair reversal learning. Behavioral effects might include misinterpretation of social and emotional information, faulty interpretation of emotion in others, impaired emotional processing of affective memories, and difficulty inhibiting inappropriate social responses (e.g., aggressive impulses). Similarly, high levels of stress-induced glucocorticoids are likely to impair working memory and to augment synaptic catecholamine levels, which likely would lead to a further engagement of postsynaptic alpha$_1$ receptors. On the other hand, stress-induced release of DHEA might enhance PFC functioning by direct effects on GABAergic and NMDA receptor function as well as indirect effects on monoamine release.

In this chapter, we have also reviewed data showing that NE, seroto-

nin, and cortisol have important effects on the amygdala. For example, high levels of stress-induced catecholamines and cortisol enhance functioning of the amygdala (e.g., enhanced fear conditioning and consolidation of emotional memories) while low levels of serotonin reduce the threshold of amygdala firing through effects on GABA. In addition to orchestrating the fear response, the amygdala also modulates the neurochemical environment of the PFC.

Taken together, findings from preclinical and clinical studies suggest that alterations in NE, 5-HT, and adrenal hormones may contribute to psychological symptoms and neuropsychological deficits described in patients with PTSD through effects on multiple brain regions including the PFC and amygdala. Reduced serotonin (through effects on the orbitofrontal cortex), elevated NE (through actions at the postsynaptic alpha$_1$-adrenergic receptor) and cortisol (through interactions with catecholamines) may all contribute to impaired PFC functioning, including reduced inhibition of the amygdala. Decreased inhibition by the PFC, in combination with excitation secondary to elevated levels of catecholamines and cortisol, and reduced levels of 5-HT, would leave the amygdala in an activated and "unleashed" state. Activation of the amygdala, in the presence of impaired PFC executive functioning, might activate release of NE (LC), dopamine (ventral tegmental area) and acetylcholine (dorso lateral tegmental nucleus); diminish capacity for rational problem solving and rational influence on behavior and thought; exaggerate the startle response; increase fear conditioning; enhance consolidation of emotional memory; and increase vigilance, insomnia, impulsivity, intrusive memories, flashbacks, and other fear-related behaviors.

We have also focused in this chapter on the PFC and amygdala. Clearly, other brain regions such as the anterior cingulate cortex and the hippocampus play an important role in mediating stress-induced effects of neurotransmitters/neurohormones. For example, preclinical and clinical studies have clearly demonstrated a relationship between chronic stress and hippocampal function. In animals, inescapable stress has been associated with hippocampal damage and inhibition of neurogenesis. Some human studies have reported reduced hippocampal volume and deficits in hippocampal-based declarative verbal memory among subjects with PTSD. Further, in a recent study of women with PTSD, Vermetten and colleagues found a significant increase in hippocampal volume and verbal memory after long-term treatment with the SSRI paroxetine (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003). Finally, pretreatment with an SSRI has been shown to prevent the development of many fear-induced behaviors in animals. This effect is probably mediated through activation of post-synaptic 5-HT 1A receptors (reviewed in Bonne, Grillon, Vythilingam, Neumeister, & Charney, 2004).

The discussion in this chapter has potential clinical implications (see Friedman, Chapter 13, this volume). For example, alpha$_2$-adrenergic receptor agonists (e.g., clonidine, guanfacine) might be helpful through effects on presynaptic alpha$_2$ receptors in the LC (reduced NE release and reduced NE stimulation of the amygdala) as well as increased occupancy of prefrontal cortical alpha$_2$-adrenergic receptors (enhanced PFC function and inhibition of the amygdala). Alpha$_1$-adrenergic-receptor antagonists (e.g., prazosin) might help by reducing NE occupancy of alpha$_1$-adrenergic receptors (decreased impairment of PFC functioning and improved inhibition of the amygdala). SSRIs might exert positive effects by increasing orbitofrontal cortex inhibition of the amygdala and by increasing threshold of amygdala firing through effects on GABA. CRF antagonists might also reduce trauma-related symptoms and cognitive deficits through effects on multiple brain regions, neurotransmitter and neuropeptide systems, and the HPA axis.

It is important to note that the above discussion is speculative in nature since direct evidence for these ideas is largely lacking in clinical populations. It is also important to remember that the relationship between neurobiology and behavior is exceptionally complex. In discussing only three neurotransmitters/neurohormones, we have presented an incomplete and extremely simplistic model. Much research remains to be conducted on the interface between trauma-related neurotransmitter/neurohormone alterations, regional brain function, psychological symptoms, and neuropsychological deficits in trauma survivors with PTSD.

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